CLINICAL AND METABOLIC STUDIES OF A CASE OF HYPOPITUITARISM DUE TO CYST OF THE HYPOPHYSIS WITH INFANTILISM OF THE LORAIN TYPE (SO-CALLED TYPUS FROEHLICH OR ADIPOSO-GENITAL DYSTROPHY OF BARTELS).

By De Witt Stetten, M.D.,
ASSISTANT VISITING SURGEON TO THE GERMAN HOSPITAL; INSTRUCTOR IN CLINICAL SURGERY IN COLUMBIA UNIVERSITY, NEW YORK CITY,
AND
Jacob Rosenbloom, M.D., Ph.D.,
ASSISTANT PROFESSOR OF BIOLOGICAL CHEMISTRY AT THE UNIVERSITY OF PITTSBURGH, PITTSBURGH, PA.

Introduction. Through the efforts of Cushing, Goetsch, and Jacobson considerable light has been thrown on our knowledge of the function of the pituitary gland, especially in its diseased states. Our biochemical knowledge of this gland is scanty, and most of the work conducted has been in relation to the study of the metabolism in animals after extirpation and in acromegaly. Schiff[1] found no increase in the nitrogen of the urine in acromegaly, but did find an increase in the phosphorus of the feces. Moraczewski[2] found a retention of nitrogen, phosphorus, calcium, magnesium, and chlorine in acromegaly. Oswald[3] found that feeding pituitary extract to a dog had no effect on the nitrogen or phosphorus. Thompson and Johnson[4] found that pituitary substance stimulates metabolism in the dog to an increased degree, as shown by the output of nitrogen, urea, and phosphorus in the urine and also in the decline of the body weight.

Malcolm[5] found that the fresh whole gland increased the output of nitrogen. Benedict and Homans[6] found that the removal of the pituitary gland of dogs produced a tendency to retard the normal growth of the animal and a marked fall of the total metabolism as measured by the carbon-dioxide production. Aschner[7] found that total hypophysectomy in dogs caused a falling off in the nitrogen metabolism and the total metabolism of the fasting animal. The relation of the pituitary body to carbohydrate tolerance has been carefully studied by Goetsch, Cushing, and Jacobson.[8] Von Narbut and others in v. Bechterew's laboratory observed after hypophysectomy a diminution in the carbon-dioxide output, slight diminution in the oxygen intake, an enormous loss of water, and marked increase in the excretion of nitrogen and phosphorus. Wolf and Sachs[9] found after extirpation of part of the anterior lobe and all of the posterior lobe a distinct lowering of the carbon-dioxide output, and after removal of the anterior lobe only a lowered carbon-dioxide output, while after complete hypophysectomy they found a marked decrease in the carbon-dioxide output and an unusually low nitrogen output.

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[1] Wien. klin. Woch., 1897, x, 277; Zeitsch. f. klin. Med., 1897, xxxii, Suppl., p. 289.

[2] Zeitsch. klin. Med., 1901, xliii, 336.

[3] Virchow's Archiv, 1902, clxix, 44.

[4] Jour. Phys., 1905, xxxiii, 189.

[5] Ibid., 1904, xxx, 270.

[6] Jour. Med. Research, 1912, xxv, 409.

[7] Wien. klin. Woch., 1909, xxii, 1730, Verhand. d. Deutsch. Gesell. f. Chir., 1910, xxxix, 46.

[8] Johns Hopkins Hosp. Bull., 1911, xxii, 165.

Edsall and Miller[10] noted a retention of nitrogen and phosphorus in two patients with acromegaly. Franchini[11] found a retention of nitrogen, calcium, and magnesium in a patient with acromegaly; while the sulphur, chlorine, and phosphorus metabolism was normal. Mendel[12] also found a retention of nitrogen and a change in chlorine and phosphorus metabolism. Tauszk and Vas[13] found a slight retention of nitrogen and phosphorus and an increased calcium output. On giving pituitary tablets, no influence was exerted on the general metabolism.

Oberndorfer[14] after careful observations on a patient with acromegaly formed no definite conclusion regarding the character of the metabolism, and was inclined to doubt the finding of definite abnormalities of metabolism in acromegaly. Franchini[15] found extracts of pituitary body of cattle and horse caused a marked loss of calcium, magnesium and phosphorus excretion when injected intravenously into rabbits and guinea-pigs. Mochi[16] found that the subcutaneous injection of pituitary gland caused in rabbits a slight loss of nitrogen and a marked loss of calcium and phosphorus. Medigreceanu and Kristeller[17] studied the general metabolism, with special reference to the mineral metabolism in a patient suffering from acromegaly complicated with glycosuria, and found that the glycosuria followed the usual course of this symptom, while the carbohydrate tolerance was in no way affected by injections of the extract of the anterior lobe of the hypophysis, there was noted a general rise of metabolism after the injection. There also resulted from the injection peculiarities in salt metabolism which could not be interpreted on the basis of the rise of the general metabolism.

None of the experimental work that has been conducted on the question of metabolism in perversions of the pituitary gland can be compared with the study we describe in this paper. As may be noted in the case report, the patient is a classical type of hypopituitarism the opposite of acromegaly (hyperpituitarism), the condition which has been the subject of the several metabolic studies mentioned before.

[9] Proc. Soc. Expt. Biol. and Med., 1910, viii, 36.

[10] Univ. of Penna. Med. Bull., 1903, xvi, 143.

[11] Bioch. Zentral., 1905, p. 522.

[12] Deutsch. med. Woch., 1906, p. 1975.

[13] Jahr. f. Neurol., 1899.

[14] Zeitsch. f. klin. Med., 1908, lxv, 6.

[15] Berl. klin. Woch., 1910, pp. 613, 670, 719.

[16] Riv. di patol. nerv. e ment., 1910, xv, 457.

[17] Jour. Biol. Chem., 1911, ix, 109.

CLINICAL DATA. Hypopituitarism due to cyst of the hypophysis, with progressive bitemporal hemianopsia leading to optic atrophy and infantilism of the Lorain type (so-called typus Froehlich or adiposo-genital dystrophy of Bartels). Kanavel operation.

B. S., male, aged twenty-two years, native of Hungary, unmarried, was admitted to the surgical service of the German Hospital, New York, February 3, 1912.

Family History. The patient has three brothers and three sisters. They are all alive and well, and the men are above the average height. No other member of the family is afflicted in the same manner as the patient. There is no history of consanguinity, alcoholism, lues, tuberculosis, or cancer.

Previous History. The patient had measles and chicken-pox when a child.

Present Illness. When the patient was about ten years old it was noticed that he was not growing normally. Up to this time he had suffered from enuresis, which ceased at his eleventh year. He also began to complain of headaches, which were so severe that they prevented him from playing with other children, and even kept him awake at nights. His eyes watered considerably, and when he was thirteen years old it was discovered that his sight was so poor that he could no read the blackboard at school. Since then his eyesight has been gradually getting worse, so that now he is practically blind. His headaches have continued, and are dull and frontal in character. His physical development has been greatly retarded. He is very irritable. There has never been any indication of sexual power, neither libido, erection, nor ejaculation. There has never been nausea nor vomiting, dizziness, vertigo, loss of consciousness, nor convulsions. He has never shaved. Appetite is poor. Bowels are constipated. Micturition: diurnal 3, nocturnal 1. No polyuria. Some polydipsia. Chief complaints, blindness, headache, arrested development.

Status Praesens. General (Figs. 1 and 2): The patient is a much underdeveloped, but not poorly nourished male. He is 137 cm. (4½ feet) tall and weighs sixty-six pounds. His size is about that of a child of nine or ten years of age. He is somewhat pale and sallow, and his skin is dry. There are no eruptions nor adenopathies. There is a moderate adiposity. The mentality is sluggish, but the patient is not unintelligent nor illogical. There is no trace of imbecility. He talks little, but answers intelligently. The hair on his head is normal, but the patient has not the trace of a beard nor moustache, and no pubic nor axillary hair.

Head: The nose, mouth and pharynx are normal. The ears are rather large, but the hearing is normal. The head measures 55 cm. in circumference. The olfactory nerves are normal, as are all the other cranial nerves, with the exception of the optic. The teeth are in fair condition, and with the exception of the third molars have all erupted. The thyroid is small.

Eyes: The right eye is totally blind. With the left eye the patient can count fingers at one foot. The visual field, however, is much contracted, the temporal half being entirely absent. The pupils are of equal size and are large. There is no consensual nor direct reaction to light from the right eye. In the left eye both reactions are normal. The reaction is much more prompt and effectual from the nasal side. The refractive media of both eyes are clear. The disk of the right eye is white and the retinal vessels are well defined. The opthalmoscopic examination of the left eye gives much the same picture. Diagnosis by Dr. Schirmer: primary optic atrophy.

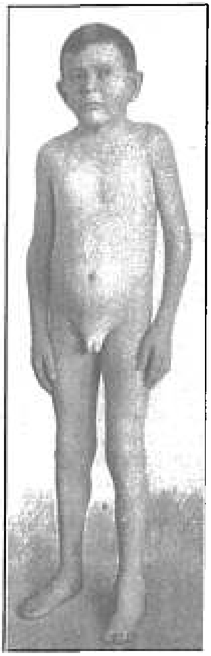

FIG. 1.—Note infantile genitals and absence of facial and pubic hair. Taken before operation.

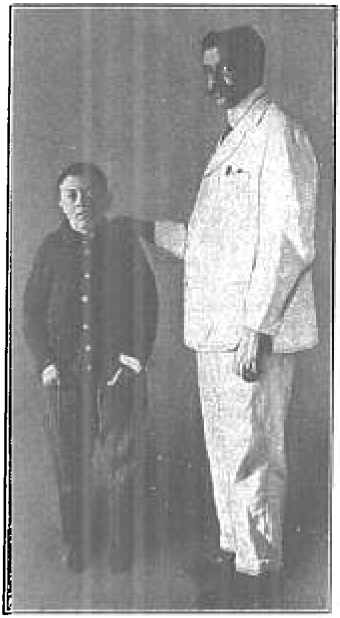

FIG. 2.—Taken nine months after operation. Orderly is of average height, five feet eleven inches. Note absence of facial deformity from operation.

Chest: Small, round, symmetrical. No deformities. No enlargement of thymus.

Lungs: Breathing over left lung normal. Rather harsh breathing, with slightly increased vocal fremitus and slight dulness over the middle lobe of the right lung. Over the upper lobe, posteriorly, on the right side a few crepitant rales may be heard.

Heart: Apex sounds normal. Aortic second somewhat accentuated. Heart action regular, percussion normal.

Abdomen: Soft, symmetrical. No abnormal masses, no areas of tenderness nor rigidity.

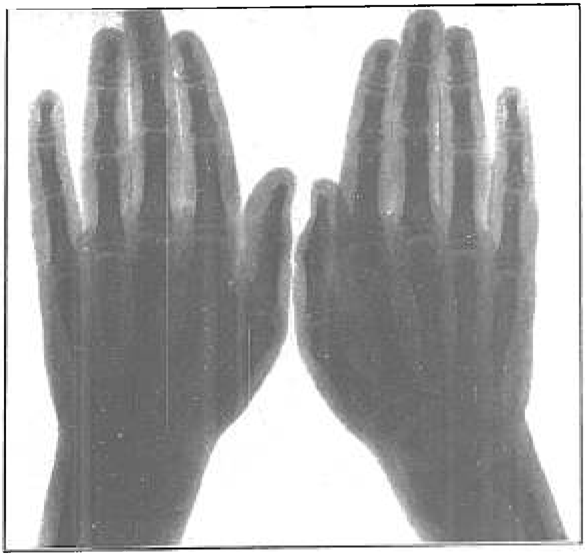

FIG. 3.—*X*-rays of hands and wrists, showing marked arrest of ossification.

Extremities: Hands and feet are small and delicately formed. The fingers are tapering; the nails are well formed, but there are no crescents. The knee-jerks are sluggish. *X*-rays of hand (Fig. 3): The pisiform bones are missing and there are no sesamoid bones. The epiphyses of the phalanges, metacarpals, radius, and ulna are just beginning to unite. The ossification of the bones of the hand corresponds about to that of a boy eleven or twelve years old.

Genital Organs: The penis is small, and the testicles, though present in the scrotum, are exceedingly undeveloped. They measure about 1 cm. in their long diameter. There are no hernias.

Nervous System: Aside from the above-described condition of the eyes there are no abnormalities of the nervous system.

Measurements: From umbilicus to crown, 51 cm.; From umbilicus to soles, 86 cm.; from umbilcus to external malleolus, 77.5 cm., both equal; arms, 22.5 cm., both equal; forearms, 18.5 cm., both equal; from anterior superior spine to internal malleolus, 73.5 cm., both equal; from ulnar styloid to tip of little finger, 14.5 cm., both equal.

Temperature, 99°; pulse, 112, soft and regular; respiration, 24. Blood pressure, 70 mm. of mercury.

Urine: 1260 c.c., acid; amber; clear; specific gravity, 1022; no protein; no sugar. The carbohydrate tolerance is greatly increased, the patient taking as much as 400 grams of glucose without sugar appearing in the urine.

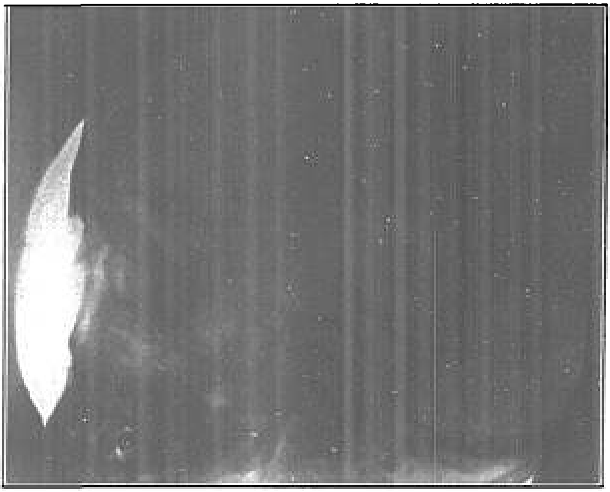

FIG. 4.—*X*-ray of skull, showing erosion of dorsum of sella turcica and posterior clinoid processes.

Blood count: Red corpuscles, 3,900,000; hemoglobin, 55 per cent.; white corpuscles, 10,000; polynuclears, 65 per cent.; large lymphocytes, 1 per cent.; small lymphocytes, 28 per cent.; mononuclears, 5 per cent.; eosinophiles 1 per cent.

The Wassermann reaction is negative.

X-ray examination of the skull (Fig. 4) shows an erosion of the dorsum of the sella turica and of the posterior clinoid processes.

There also seems to be an erosion of the posterior wall of the sphenoidal sinus.

We have here a classic case of infantilism of the Lorain type, with symptoms definitely pointing to a benign tumor, probably a cyst of the hypophysis. The general pressure symptom of headache and the distinct neighborhood signs—namely, the primary optic atrophy, apparently beginning as a bitemporal hemianopsia, and the *x*-ray picture of the skull—made this rather clear. We were obviously dealing with an exquisite case of hypopituitarism beginning in early life. The arrest of body growth and of sexual development, with the moderate adiposity, stamped this case as a typical example of the Froehlich typus or the so-called dystrophia adiposo-genitalis of Bartels. The glandular symptoms are, in the main, due to a deficiency of the anterior lobe of the pituitary gland, although it is evident that the posterior lobe function is also diminished, as indicated, by the high carbohydrate tolerance and the unusually low blood pressure.

In the hope of improving the eyesight and avoiding the threatened total blindness, and incidentally relieving the headaches, operation was decided upon.

Urotropin given and nasal cavity irrigated as a preliminary measure. February 21, 1912, operation by Dr. F. Kammerer. Preliminary inferior tracheotomy. Thyroid gland apparently normal. Ether anesthesia through tracheotomy opening. Pharynx packed with gauze through mouth.

Kanavel's infranasal sublabial trans-sphenoidal approach. A transverse incision was made at the reflexion of the mucous membrane of the upper lip on the alveolar process. The tissues were then elevated and the nasal cavity entered. The cartilage of the septum was incised anteroposteriorly at its junction with the palatal process of the superior maxilla. The cartilage was not removed. The nose was retracted upward. Both inferior and middle turbinates, vomer, and vertical plate of the ethmoid were removed with a rongeur. The bleeding, which was remarkably insignificant, was easily controlled by adrenalin tampons. The anterior wall of the sphenoidal sinus was now clearly seen and removed. The exposure was excellent and there was ample room. As soon as the sinus was opened there was a gush of about an ounce of turbid serous fluid. This was obviously the contents of a cyst, which had eroded the posterior wall of the cell. The fluid was clearly not from the cerebrospinal cavity, as the discharge ceased promptly after it was mopped up and the pulsating dura was seen intact in the depths of the wound.

It was now decided that it would be inadvisable to do anything further as the chief object of the operation had been accomplished namely, the relief of pressure on the chiasm. The cavity was packed with two small iodoform tampons, one of which was led out through each nostril. The sublabial incision was carefully sutured with silk.

The fluid from the cyst was sterile. It was not possible to obtain sufficient material for proper cytological or chemical examination.

February 23. Tampons removed from nose.

February 24. Tracheotomy tube removed.

February 25. Irrigation of nasal cavity with saline started.

The patient stood the operation well and reacted promptly. Twenty-four hours after operation the temperature rose to 103°; with pulse of 110, and remained so for five days. Then the temperature and pulse gradually came down, but again rose on the ninth day. From this time there were irregular rises and falls of temperature from 103.5° to 100° for nine weeks following the operation. The patient was drowsy, slept most of the time, ate very little, vomited frequently, complained of headache, looked pale, and began to get edema of the face, hands, and feet. He was put on large doses of urotropin.

In spite of constant irrigation of the nasal cavities there was a profuse purulent discharge, especially from the right side. There was no rigidity of the neck, no increased reflexes, and no Kernig symptom.

March 3. Anterior lobe, desiccated pituitary substance, grain j, given three times daily. Discontinued March 8.

April 4. Spinal puncture. 5 c.c. of clear fluid withdrawn. No pressure. Report of Dr. Garbat: No fibrin filament on standing. Very scant sediment after centrifuging. Few cells, but insufficient in number for differential count. Few Gram positive cocci. Globulin reaction negative. Acetic acid test plus. Reduction of Fehling's faint. Cultures: Plate directly from fluid, sterile. Broth tubes from fluid show Staphylococcus albus, evidently a contamination.

The temperature remained high and the symptoms about the same for a week following the spinal puncture. The case made an unfavorable impression, and there seemed little chance of a recovery. Then the purulent discharge from the nose stopped; the temperature dropped to normal and remained so; the headache disappeared; the drowsiness cleared up; the vomiting ceased, and the appetite improved. From this point the patient made a rapid recovery. There had evidently been an extradural suppuration at the site of the old sphenoidal sinus, and this chronic suppurative process, which had been responsible for the septic and pseudo-meningitic symptoms, had now healed.

The eyesight, however, had not improved. If anything it was worse than before the operation. There was practically total blindness. There was perhaps a perception of light in the left eye. No pupillary reaction to light.

June 5. Ophthalmoscopic examination by Dr. Denig showed optic atrophy of both eyes. The outlines of the disks were sharp, the veins normal, and the arteries a trifle narrow.

The wound in the mouth healed so well that the scar can scarcely be found. There is the slightest trace of a saddle nose as the only external evidence that an operation has been performed. Nasal examination shows a large perforation due to the absence of the bony septum. The turbinates are missing and the cartilaginous septum is deviated to the left. There is a slight serous discharge from the right side.

X-ray examination of the skull reveals no marked changes in the base of the skull.

July 2. The patient was discharged from the hospital, with headaches cured.

He has improved greatly since he left the hospital. He has been examined several times since, the last time on November 20. On November 16, he was presented at the demonstration in the German Hospital to members of the Third Clinical Congress of Surgeons of North America. He looks well, has a good color, and has gained ten pounds in weight since the operation. His headaches are entirely gone and he sleeps through the night, something that he has not done in many years. His appetite is excellent. His bowels are also more regular. His mentality is more active and he is much more talkative. His disposition has changed for the better. He has entirely lost his irritability. As to the sight, there does not seem to be much objective change, though the patient and his mother think there has been some improvement. He claims to be able to see quite well at times. He is able to walk alone on the street, and insists that he sees his way and does not feel it. He claims to see better at dusk. An examination of the eyes by Dr. Schirmer shows that the ophthalmoscopic picture has not changed. The right eye is blind and there is no pupillary reaction. With the left eye the patient can see movements of the hand and the pupil reacts normally. The nose is entirely healed and there is no more discharge. There has been no evidence of growth since the operation. The *x*-ray of the hand shows exactly the same condition as before.

The patient has been put on desiccated pituitary substance (anterior lobe), grains ij, three times a day, after meals.

METABOLIC DATA. *Methods.* Nitrogen determinations were made by the Kjeldahl method, the ammonia by the Folin method, urea by Benedict's new method,[18] uric acid by the Folin-Shaffer method, total sulphur by Benedict's method;[19] creatinin by Folin's method, total sulphates by Folin's method, inorganic sulphates by Folin's method. The ethereal sulphates were estimated by subtracting the inorganic sulphates from the total sulphates and neutral sulphur by subtracting the total sulphate-sulphur from the total sulphur.

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[18] Jour. Biol. Chem., 1910, viii, 405.

[19] Ibid., 1909, vi, 363.

Samples of milk used in the diet were analyzed for nitrogen and fat. The nitrogen of the weighed eggs (minus shell) was computed with the aid of the figure given by Koenig (2.008 per cent. nitrogen). The feces were marked off by means of carmine into periods of three days. The fat content of the feces was determined by the method of Kumagawa and Suto.[20]

The patient was placed on Folin's diet,[21] consisting of:

Whole milk	500 c.c.
Cream (18 to 22 per cent. fat)	300 c.c.
Eggs (whole)	450 gm.
Horlick's malted milk	200 gm.
Sugar	20 gm.
Sodium chloride	6 gm.
Water	2100 c.c.

This diet contains approximately 119 gm. protein, 148 gm. fat, 225 gm. carbohydrate, yielding 2787 calories.

The following tables contain the results obtained in this study, and it may readily be noted that the absorption of protein and fat was normal in this individual, while the proportion of nitrogen of the urine as undetermined nitrogen and the proportion of sulphur of the urine as neutral sulphur are regularly much higher than the normal.

TABLE I.—(Nitrogen Partition) Urine.

Date.	Total nitrogen grams.	Urea nitrogen.		Ammonia nitrogen.		Creatinin nitrogen.			Uric acid nitrogen.		Undetermined nitrogen.	
		Grams.	Per cent. of total nitrogen.	Grams.	Per cent. of total nitrogen.	Grams.	Per cent. of total nitrogen.	Co-efficient. Milligrams.	Grams.	Per cent. of total nitrogen.	Grams.	Per cent. of total nitrogen.
June 23	13.0											
June 26	16.1	13.5	83.8	0.36	2.3	0.60	3.8	20	0.20	1.4	1.4	8.7
June 27	16.3	13.3	81.6	0.41	2.5	0.58	3.5	19+	0.24	1.5	1.8	11.0
June 28	15.7	12.6	80.3	0.40	2.5	0.56	3.5	18+	0.26	1.7	1.9	12.1
June 29	15.8	12.9	81.7	0.44	2.7	0.54	3.4	18	0.23	1.5	1.7	10.8
June 30	15.3	12.3	80.5	0.40	2.6	0.50	3.3	16+	0.27	1.7	1.8	11.7
July 1	15.7	12.6	80.2	0.48	3.1	0.55	3.5	18+	0.29	1.9	1.8	11.5

TABLE II.—(Sulphur Partition) Urine.

Date.	Total sulphur grams.	Total sulphate sulphur, grams.	Ethereal sulphate sulphur, grams.	Inorganic sulphate sulphur, grams.	Neutral sulphur, grams.	Sulphate sulphur. Total sulphur. Per cent.	Ethereal sulphate sulphur. Total sulphur. Per cent.	Inorganic sulphate sulphur. Total sulphur. Per cent.	Neutral sulphur. Total sulphur. Per cent.
June 23	0.57	0.45	0.04	0.41	0.12	78.6	6.8	71.8	21.3
June,26	0.41	0.30	0.03	0.27	0.11	72.5	7.2	65.3	27.4
June 27	0.80	0.66	0.06	0.60	0.14	82.4	7.1	75.3	17.5
June 28	0.90	0.69	0.04	0.65	0.21	76.7	4.3	72.4	23.3
June 29	0.90	0.69	0.05	0.64	0.21	76.7	5.5	71.1	23.3
June 30	0.87	0.53	0.05	0.48	0.34	61.7	6.4	55.3	38.3
July 1	0.96	0.66	0.04	0.63	0.30	69.2	4.0	65.2	30.8

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[20] Biochem. Zeit., 1908, v. 212.

[21] Amer. Jour. Physiol., 1905, xiii, 45.

TABLE III.—Summary of Data Pertaining to Total Nitrogen and Fat Metabolism.

Date.	Total nitrogen.			Feces.			Fat.	
					Total nitrogen.			
	Ingested grams.	Excreted grams.	Balance grams.	Fat grams.	Found grams.	Per cent. of total nitrogen ingested.	Ingested grams.	Absorbed grams.
June 26 . . .	18.2	17.9	+0.3	2.2	1.8	9.9	140.0	137.8
June 27 . . .	18.6	18.1	+0.5	2.2	1.8	9.7	140.0	137.8
June 28 . . .	18.3	17.5	+0.8	2.2	1.8	9.9	140.0	137.8
June 29 . . .	18.1	17.9	+0.2	1.8	2.1	11.6	146.0	144.2
June 30 . . .	17.6	17.4	+0.2	1.8	2.1	11.9	146.0	144.2
July 1 . . .	17.8	17.8	0.0	1.8	2.1	11.9	146.0	144.2
Total	108.6	106.6	+2.0	12.0	11.7	....	858.0	846.0
Average	18.1	17.7+	+0.33	2.0	1.95	10.8	143.0	141.0

DISCUSSION OF METABOLISM RESULTS. During the six days on the standard diet it may be noted that the patient showed a slight retention of nitrogen, while the absorption of fat and protein was normal in degree. The percentage of the various urinary constituents were normal, with the exception of the neutral sulphur and undetermined nitrogen. The undertermined nitrogen of the urine is made up of substances present in variable amount and difficult to estimate. In this fraction are present various monamino and diamino-acids, hippuric acid, oxyproteic and alloxyproteic acids, allantoin and possibly other substances not yet defined. On a diet yielding about 16 grams of total nitrogen in the urine, Folin has shown that the undetermined nitrogen of normal urine is about 4 per cent. of the total nitrogen. The nature of the neutral sulphur of the urine is also uncertain; it may be made up of the sulphocyanates from the saliva, hydrogen sulphide, cystein, an intermediary compound of normal protein metabolism and taurocarbamic acid from bile. Traces of chondroitin-sulphuric acid and, oxyproteic acids also help make up the neutral sulphur content of the urine. Cystin, if present, would also increase the neutral sulphur. Folin has shown that the neutral sulphur of the urine is made up of substances, which in the main are independent of the total amount of sulphur eliminated or of protein catabolized and variations in the neutral sulphur of the urine, must be regarded as showing presence of abnormal metabolic processes, which are not associated with variations in the other types of urinary sulphur. On the diet given to this patient the neutral sulphur should not normally be higher than 10 to 12 per cent. of the total urinary sulphur.

We therefore have in this case a marked perversion of some metabolic process leading to high and abnormal percentages of the neutral sulphur and undertermined nitrogen of the urine. Our knowledge of these two groups of substances is very meager, and it would be unwise at present to attempt any specific explanation of this anomaly.